REMARKS

Applicants have amended the claims and respond to the Restriction Requirement as discussed more fully below.

Response To Restriction Requirement

In the Transmittal Letter filed with this application on June 7, 1995, applicants cancelled original claims 1-15, 18-19 and 21-22 of the application. Accordingly, the claims pending at the time of the Restriction Requirement were claims 16-17 and 20. Those claims are directed to HLA typing processes and kits.

The Restriction Requirement treated all of original claims 1-22 as pending. By Preliminary Amendment herein, applicants have added claims directed to subject matter included in or based on original claims 1-2, 4, 9-10, 14-15 and 19. The corresponding added claims are 23-24, 25, 26-27, 28-29 and 30. All of these added claims, as well as added claims 31-47 discussed below, are directed to subject matter included in Group I of the Restriction Requirement, to which applicants respond below.

Claims 1-22 stand subject to restriction in this application under 35 U.S.C. § 121 into two Groups, considered by the Examiner to be patentably distinct. These Groups, and their corresponding claims, are:

I. DNA sequences, HLA typing processes, HLA typing kits comprising such sequences, processes for producing such sequences and processes for producing proteins expressed by such sequences (claims 1-10 and 14-20); and

II. Polypeptides displaying an immunological or biological activity of at least one ß-chain antigen and HLA-DR typing kits including polypeptides raised against those polypeptides (claims 11-13 and 21-22).

Applicants elect the subject matter of Group I for initial substantive examination in this application. This election is expressly without waiver of applicants' right to continue to prosecute and to obtain claims to the subject matter of the non-elected Groups in applications claiming priority herefrom.

The Claim Amendments

Applicants have amended claims 16 and 20. In addition, applicants have added claims 23-47. All of the added claims are directed to the elected subject matter. None of these amendments constitutes new matter.

Claims 23 and 24 include DNA sequences which, upon expression, code for a portion of a polypeptide encoded by any one of the recited DNA inserts, said portion comprising a region of mismatch between polypeptides coded for by any two of those inserts, and which hybridize under high criteria to any of the foregoing DNA inserts. These amendments are supported in the application at page 32, lines 1-30.

As part of that disclosure, applicants determined and compared the nucleotide sequence of the DR-ß-A and DR-ß-B inserts of this invention (the sequences of which are disclosed in Figures 5A-5D, 7 and 7A) and identified nucleotide sequence differences that, upon expression, coded for regions of amino acid mismatch between the polypeptides coded for by those inserts. See, e.g., page 32, lines 1-8 and Figure 9. Applicants also taught one of skill in the art to analyze and compare the nucleotide sequences of the other HLA-DR-ß chain inserts of this invention to identify the DNA sequences that code for regions of mismatch between the polypeptides encoded by those inserts. See, e.g., specification, page 32, lines 23-

30. Applicants have taught that DNA sequences comprising such sequence differences are useful to distinguish between the genomic DNAs of individuals of different HLA-DR specificities (specification, page 32, lines 12-30).

Also, applicants have taught that the DNA sequences useful in the typing kits and processes of this invention hybridize under high criteria to one of the DNA inserts of this invention. Those of skill in the art, in view of applicants' teaching, would appreciate that only DNA sequences having a high degree of homology with one of the DNA inserts of this invention would hybridize under high criteria.

Claims 23-24 and 29 do not recite the phrase "said DNA sequences encoding a product that displays immunological or biological activity of a ß-chain antigen" (formerly recited in original claims 1-2 and 15). The recited DNA sequences are useful in the typing processes and kits of this invention because they hybridize to particular HLA-DR DNA sequences in an individual's genomic DNA. Thus, the DNA sequences, full-length and fragments, recited in the claims, have utility in and of themselves. While the products encoded by such DNA sequences may have an "immunological or biological activity of a ß-chain antigen", such an activity is not required for DNA sequences useful in the processes and kits of this invention. For example, the six DNA sequences depicted in Figure 9 are useful in HLA-DR typing processes and kits according to this invention, regardless of whether they encode products displaying an immunological or biological activity of a ß-chain antigen.

Claim 25 recites other DNA sequences useful in typing processes and kits according to this invention. These DNA

sequences include the 19-mers formerly recited in original claim 4, adding two additional 19-mers depicted in Figure 9 and formerly recited in original claim 18.

The application also discloses that fragments and portions of applicants' DNA inserts, including portions of the regions of amino acid mismatch, are useful in HLA β typing kits and processes. Claims 31-37 include such fragments and portions.

More particularly, as set forth in the specification:

> "The cDNA inserts coding for families of HLA-DR-ß-chain antigens or fragments thereof may be used in DR typing processes and kits. In general such typing processes comprise the steps of ... (3) hybridizing the size fractionated DNA to the HLA/DR-ß-chain related probes of this invention or fragments thereof and ...." (specification, page 29, lines 10-19, emphasis added).

With applicants' disclosure in hand and in view of knowledge in the art as of applicants' effective filing date, one of skill in the art could readily prepare fragments of the DNA inserts and sequences of this invention useful for HLA β typing processes and kits.

As of the effective filing date of this application, the ordinary skilled worker would appreciate that, in any specific DNA typing kit or DNA typing process, the useful DNA sequences are those that hybridize selectively to the DNA sequence of interest. Those of skill in the art would also appreciate that a DNA sequence that encodes only a single amino acid, or even two or three amino acids, would not be specific enough to be useful in a DNA typing kit or process. Such a short DNA sequence would hybridize to many DNA sequences that comprise that short sequence. It would also be routine for one of skill in the art to determine the length of a DNA sequence that will specifically hybridize to a particular DNA sequence

in the human genome. Thus, once provided with a particular DNA sequence, such as those recited in the amended and added claims, one of skill in the art would be readily able to prepare a DNA sequence or fragment of that DNA sequence that would specifically hybridize to DNA of interest.

Applicants were the first to disclose particular DNA sequences and inserts that code for specific HLA-DR-ß chain polypeptides. Thus, applicants were the first to make it possible for anyone of skill in the art to prepare and use HLA-DR-ß chain specific DNA sequences to determine, on a DNA level, the HLA-DR-ß specificity of an individual's DNA.

Applicants have taught that DNA fragments that are identical among the disclosed DNAs and DNA fragments that comprise regions of mismatch between any two of the DNA inserts will be useful in the DNA typing kits and processes of this invention.

> "In like manner, a collection of 19-mer DNA probes from regions of mismatch and identity among the other HLA-DR-ß chain genes may be prepared. Each of the probes will then be specific for a given DR specificity. Hybridization with the collection of probes and controls would, accordingly, allow the rapid and accurate DR typing of large numbers of individuals." (specification, page 32, lines 23-30).

For example, fragments that are common to all the DNA inserts of this invention will hybridize to the homologous HLA-DR sequences in the genomic DNA of all individuals. Fragments from regions of mismatch will be unique to a particular insert and will hybridize only to the homologous sequences in the genomic HLA-DR fragment of an individual having a particular HLA-DR type. The HLA-DR-ß DNA sequences and fragments thereof would hybridize specifically to the HLA-DR-ß DNA sequences in the digested genomic DNA. As demonstrated in Figure 8, digestion of genomic DNA of individuals having different HLA-DR

specificities produce unique restrictions patterns detected by hybridizing the genomic DNA to the DNA inserts of this invention. Thus, one of skill in the art could easily determine an individual's HLA-DR type by comparing the pattern of hybridization between the DNA sequences of this invention -- both the full-length HLA-DR sequences and fragments thereof -- and the size-fractionated DNA of an individual to be typed, with the areas of hybridization between those same DNA sequences and the DNA of an individual of known HLA-DR type.

Based on such disclosure, applicants have added claims 31-32 and 34-35, which recite DNA sequences that code for a polymorphic region of either a Class II ß-chain locus or an HLA DR-ß chain locus. Those DNA sequences correspond to DNA sequences encoding amino acids 8-14, 26-32 or 72-78 of that locus. Support for these claims is found on page 32, lines 5-8 and in Figure 9. Applicants have also added claims 33, 36 and 37, which recite DNA sequences that code for a conserved region of an HLA DR-ß chain locus corresponding to the DNA sequence encoding amino acids 39-45 of that locus. Page 32, lines 9-11 of the specification identifies that DNA sequence as one identical among the DR-ß chain genes. Added claims 46 and 47 recite HLA-DR typing kits in which a 19-mer from within that region serves as a hybridization control. This claim is supported by original claim 19.

Added claim 40 is directed to HLA-DR typing kits comprising the DNA sequences of any one of claims 31-33.

Added claims 38-39 recite particular DNA sequences corresponding to, respectively, the expressed portions of the DNA inserts DR-ß-A and DR-ß-B.

Finally, applicants have added claims 41-45, directed to HLA-DR typing processes according to this invention. As discussed above, applicants have discovered the utility of various DNA sequences to determine HLA-DR specificity of a given sample at the DNA level, using hybridization techniques. The patentability of applicants' HLA-DR typing processes based on that discovery is independent of steps relating to preparation of the sample to be typed or comparison of areas of hybridization between the sample and the particular HLA-DR specific DNA sequence to areas of hybridization between DNA of known HLA-DR type and that DNA the sample and that DNA sequence. Accordingly, applicants are entitled to process claims reciting these steps separately, or in combination.

Supplemental Information Disclosure Statement

Pursuant to 37 C.F.R. §§ 1.56 and 1.97, applicants make of record the following documents, copies of which are submitted herewith:*

United States Patents

5,541,065 (Erlich et al.) issued July 30, 1996

5,468,613 (Erlich et al.) issued November 21, 1995

5,310,893 (Erlich et al.) issued May 10, 1994

PCT Patent Application

PCT WO 92/10589, published June 25, 1992

PCT WO 92/11389, published July 9, 1992

Applicants respectfully request that the above-cited documents be (1) fully considered by the Examiner during the

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* For the Examiner's convenience, applicants have enclosed a completed Form PTO-1449, listing these documents.

course of the examination of this application and (2) printed on any patent issuing from this application. Applicants also request that a copy of the enclosed Form PTO-1449, duly initialed by the Examiner, be forwarded to the undersigned with the next official communication.

This Statement is submitted more than three months from the application filing date but before the mailing date of the first Office Action on the merits. In accordance with 37 C.F.R. § 1.97, submission of this Statement requires no fee.

The Commissioner, however, is hereby authorized to charge payment of any additional fees required in connection with this Supplemental Information Disclosure Statement to Deposit Account No. 06-1075.

Applicants request favorable action in this application.

Respectfully submitted,

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